REMARKS

Claims 24, 26, 27, 29, and 37-39 are pending in the application. Claims 24, 26, 27, 29, 38, and 39 have been amended for further grammatical clarity. No new matter has been added. Applicants respectfully request entry of the above amendments, which raise no new issues that require further consideration or search, and which place the application in better condition for allowance.

The specification has been amended at paragraph [0052] to delete reference to a hyperlink. Unless otherwise indicated, paragraph numbering is based on Publication No. US 2003-0232334, which corresponds to the above-referenced application. No new matter has been added.

Applicants respectfully request reconsideration and allowance of claims 24, 26, 27, 29, and 37-39 in view of the above amendments and following remarks.

Withdrawal of Previous Rejections

Applicants acknowledge with appreciation the withdrawal of the following:

a) objection to claims 24 and 37; and

b) rejection of claims 24, 26, 27, 29, and 37 under 35 U.S.C. §112, first paragraph, for reciting new matter.

Claim Objections

The Office objected to claim 38 for omitting "diagnosing" in the preamble of the claim. Claim 38 has been amended to recite that the method is for diagnosing colon cancer. Accordingly, the Office is requested to withdraw the objection to claim 38.

Rejection under 35 U.S.C. §112, second paragraph

The Office rejected claim 38 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite with respect to the phrase "highly stringent" hybridization conditions. The Office asserted that claim 38 does not define the stringent hybridization conditions that include

"hybridization at 60C in a solution with a sodium ion concentration from about 0.01 to 1.0M, pH 7.0 to 8.3 comprising formamide" and cited to page 11 of the specification. The Office suggested amending the claims by "distinctly defining the conditions, including washing conditions, under which highly stringent conditions are practiced." Applicants respectfully disagree.

Claim 38 recites that hybridization is performed at 60°C in a solution with a sodium ion concentration from about 0.01 M to 1.0 M, pH 7.0 to 8.3 comprising formamide. Thus, claim 38 recites high stringency hybridization conditions. Furthermore, as high stringency conditions are known in the art, one of ordinary skill in the art could readily determine suitable washing conditions. See, for example, paragraph [0055] of the specification. Applicants submit that claim 38 is sufficiently definite. Accordingly, the Office is requested to withdraw the rejection of claim 38 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §112, first paragraph

The Office rejected claims 24, 26, 27, and 37-39 under 35 U.S.C. §112, first paragraph, for an alleged lack of enablement. The Office asserted that the claims are drawn to contradictory methods as "[t]he claims do not point-out whether lower levels of said nucleic acid are found in samples of a patient that is to be diagnosed as having colon cancer as compared to levels of said nucleic acid in control samples or whether the lower levels of said nucleic acids are found in the control samples as compared to a patient that is to be diagnosed as having colon cancer."

While Applicants disagree with the Office, claims 24, 27, 38, and 39 have been amended to clarify that a patient is diagnosed with colon cancer if levels of the nucleic acid are decreased in the patient sample relative to the control sample. As such, claims 24, 26, 27, and 37-39 do not encompass contradictory methods.

The Office asserted that "of the hundreds of CA nucleic acids disclosed in the specification (see Table 1), the specification does not disclose which CA nucleic acids are upregulated and which are downregulated in particular carcinomas."

The claimed methods do not relate to hundreds of CA nucleic acids. Rather, the claims relate to nucleic acids having a particular sequence, SEQ ID NO:167 or the full complement thereof, and nucleic acids at least 98% identical to the nucleotide sequence set forth in SEQ ID

NO:167. Furthermore, the claims recite that patients are diagnosed with colon cancer when a decrease in the level of the recited nucleic acid is observed relative to the control.

The Office further asserted that "the specification lacks working examples demonstrating contradictory methods wherein patients with lower levels of said nucleic acid and patients with higher levels of said nucleic acid, as compared to levels of said nucleic acid in negative controls, are diagnosed with colon cancer."

As indicated above, claims 24, 26, 27, and 37-39 relate to decreases of the nucleic acid in the patient sample relative to the control and do not encompass contradictory methods.

The Office relies on Tockman *et al.* (*Cancer Research*, 1992) to support the alleged lack of enablement. The Tockman *et al.* reference discusses the steps recommended for bringing a biomarker into clinical application, a commercial application of a biomarker. As stated in MPEP § 2164, in order to comply with 35 U.S.C. §112, first paragraph, "it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim to that effect.' *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) ..." Thus, the teachings of Tockman *et al.* are not relevant when considering whether an invention is enabled under 35 U.S.C. §112, first paragraph. Applicant submits that the standard for enablement is not a "certainty" of success, but a "reasonable expectation" of success, and that a "conclusive determination" or "irrefutable" demonstration of diagnostic efficacy is not required for patentability. The courts have consistently held that this is not the proper level of inquiry when assessing utility and enablement under Title 35. The proper standard for enablement is that the specification teaches those of ordinary skill in the art how to make and use the invention without "undue experimentation." MPEP 2164.01. Further, at no point does the Tockman *et al.* reference suggest that a biomarker that has not yet been validated for use in the clinic is not suitable as a biomarker in general. Thus, the Tockman *et al.* reference provides guidelines for validating biomarkers for commercial clinical use, but it is not relevant or instructive for evaluating whether the presently claimed invention is enabled under 35 U.S.C. § 112, first paragraph.

Applicants respectfully assert that the specification enables one of ordinary skill in the art to practice the methods of claims 24, 26, 27, and 37-39 without undue experimentation. One of ordinary skill in the art can readily determine if expression of a nucleic acid having the

nucleotide sequence set forth in SEQ ID NO:167, or a nucleic acid having at least 98% identity to SEQ ID NO:167, is decreased relative to that of a control sample. One of ordinary skill in the art also can readily determine if the amount of duplex formed upon contacting a polynucleotide that hybridizes under highly stringent conditions to a nucleic acid having the nucleotide sequence set forth in SEQ ID NO:167 or full complement thereof with a patient sample is decreased relative to the amount of duplex formed by hybridization of such a polynucleotide to a control non-cancer sample (see claim 38). The specification provides detailed guidance for detecting mRNA, e.g., at paragraphs [128] - [0133] of the specification, and for hybridization, e.g., at paragraphs [0055] and [0133] of the specification. One of ordinary skill in the art will appreciate that decreased expression of EGR1 mRNA can be used to facilitate diagnosis of colon cancer.

In view of the above, Applicants assert that the specification enables one of ordinary skill in the art to practice the methods of claims 24, 26, 27, and 37-39. The Office is requested to withdraw the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement.

CONCLUSION

It is believed that any pending objections and rejections have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify agreement with or concession of that rejection, issue, or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

Applicants submit that claims 24, 26, 27, 29, and 37-39 are in condition for allowance, which action is requested. Please apply the one-month Petition for Extension of Time fee and any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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